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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/864,637	05/23/2001	Chia-Lin Wei	00801.0197.NPUS00	1716

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EXAMINER	
STRZELECKA, TERESA E	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 05/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/864,637	WEI ET AL.	
	Examiner	Art Unit	
	Teresa E Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 January 2004 and 12 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-31,43-45 and 47-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-31, 43-45 and 47-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 26, 2004 has been entered.

2. Claims 1-8, 10-32, 37-46 were previously pending. Applicants cancelled claims 1-8, 10-14, 32, 37-42 and 46, amended claims 15, 31, 43 and 44, and added new claims 47-51. Claims 15-31, 43-45 and 47-51 are pending and will be examined.

3. Applicants' claim cancellations and amendments overcame the following rejections: rejection of claims 1-8, 10-32 and 37-46 under 35 U.S.C. 112, second paragraph; rejection of claims 1-5, 7 and 10-14 under 35 U.S.C. 103(a) over Nelson et al. and Frohman et al.; rejection of claim 6 under 35 U.S.C. 103(a) over Nelson et al., Frohman et al. and Somerville et al; rejection of claim 8 under 35 U.S.C. 103(a) over Nelson et al., Frohman et al. and El-Meanawy et al; rejection of claim 38 under 35 U.S.C. 103(a) over Nelson et al., Frohman et al. and Gress et al.; rejection of claims 39-41 under 35 U.S.C. 103(a) over Nelson et al., Frohman et al. and Xu et al.; rejection of claims 32, 37 and 46 under 35 U.S.C. 103(a) over Nelson et al. and Carninci et al.

4. The remaining rejections are maintained for reasons given in the "Response to Arguments" section below.

Response to Arguments

5. Applicant's arguments filed January 24, 2004 have been fully considered but they are not persuasive.

Applicants argue that claim 15 and the dependent claims are not obvious over the combination of Nelson et al. and Carninci et al., since (a) both Nelson et al. and Carninci et al. teach procedures of library normalization based on subtraction with drivers, and the goal of the claimed method is normalization not subtraction; (b) the drivers are not from a subgroup of high abundance clones of the library being normalized; (c) neither reference teaches separation of high abundance sample cDNAs into subgroups which are then hybridized to each other.

Regarding (a), both Nelson et al. and Carninci et al. teach library normalization (see, for example, page 214, second paragraph, of Nelson et al. and page 1618, second paragraph and page 1620, third paragraph of Carninci et al.).

Regarding (b) and (c), Nelson et al. teach identification of members of the non-normalized library present in high amounts and in low amounts, i.e., generation of subgroups, by hybridization of the library with probes obtained from the same library (page 210, third and fourth paragraph; page 211, fourth and fifth paragraphs). Carninci et al. teach normalization of libraries by hybridization of full-length cDNAs to RNA from which the cDNAs were obtained and removing the abundant cDNA-RNA hybrids (Fig. 1; page 1625, last paragraph; page 1626, 1627; page 1628, paragraphs 1-6). In addition, Carninci et al. teach preparation of minilibraries from the highly-abundant cDNAs, i.e., selecting subgroups of the highly-abundant members of the sample (page 1620, second and third paragraphs; page 1627, paragraphs 8 and 9; Table 1). The minilibraries are then used to identify more groups of highly abundant members (Table 1, see normalization of library 26-100). Therefore Nelson et al. and Carninci et al. teach all of the steps of the method of claim 15.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 15-19, 21, 23-31, 44 and 47-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nelson et al. (Genetic Analysis: Biomolecular Engineering, vol. 15, pp. 209-215, 1999; cited in the IDS and in the previous office action) and Carninci et al. (Genome Res., vol. 10, pp. 1617-1630, October 2000; cited in the IDS and in the previous office action).

A) Regarding claim 15, Nelson et al. teach construction of normalized cDNA library, the method comprising:

(a) constructing a non-normalized cDNA library from an RNA sample, wherein said RNA sample contains different species of RNA of different amounts, wherein each member of said non-normalized cDNA library is separate from other members (Nelson et al. teach construction of a non-normalized cDNA library from polyA+ RNA isolated from normal human prostate tissue (page 210, third paragraph). Nelson et al. teach that a cDNA library reflects transript diversity and redundancy of cellular mRNAs, of which 40-45% are rare transcripts, 40-45% are moderately abundant transcripts and 10-20% are highly abundant transcripts (page 209, second paragraph). Nelson et al. teach the non-normalized library having 780 different mRNA species (Table 1). Nelson et al. teach separation of members of the library by plating individual clones onto 384-well microtiter plates, grown and replica-spotted onto nylon membranes. The replicas were allowed to grow on the membranes, and

then the colonies were lysed, providing DNA bound to the membrane (page 210, third paragraph).);

(b) identifying the relative amounts of each member of said non-normalized cDNA library represented in said RNA sample (Nelson et al. teach identifying relative amounts of each of the clones of the library by hybridizing a probe derived from total prostate mRNA with the nylon membranes (Fig. 1; page 210, paragraphs 4-6).);

(c) dividing the members of said non-normalized cDNA library into groups; wherein one group of members of said non-normalized cDNA library is represented in low amounts by said RNA sample and one or more groups of members of said non-normalized cDNA library is represented in high amounts by said RNA sample (Nelson et al. teach dividing the library into groups by examining the intensities of labeled clones. Clones with signal intensities within the bottom quartile of the averaged intensities were selected as the group containing transcripts of low abundance (page 210, fifth and sixth paragraphs). A total of 842 cDNA clones were selected based on low hybridization intensities, of which 142 were discarded. Of the remaining 700 cDNA clones, 89% of sequences were genes of low abundance (= low expression) (page 211, fourth and fifth paragraphs; Table 1). Ten clones with high signal intensities, i.e., group of high abundance clones, were also identified (Fig. 1).).

Regarding claims 16-19 and 21, Nelson et al. teach isolation of polyA+ RNA from normal human prostate cells. Nelson et al. do not specifically say that the RNA was mRNA, but only mRNA in the eucaryotic cells is polyadenylated (page 210, third paragraph).

Regarding claims 24 and 25, Nelson et al. teach reverse transcription of the polyA+ RNA isolated from normal human prostate tissue using oligo-dT-30 primer, reverse transcriptase, dATP,

dTTP, dCTP, dGTP and ^{32}P-dCTP, in a reaction at 42 °C for 30 minutes (page 210, fourth paragraph).

Regarding claim 27, Nelson et al. do not explicitly teach transformation of the members of non-normalized cDNA library into host cells, but since they do have clones, these could have been obtained only by transforming the library into host cells. See also Nelson et al. (Genomics, vol. 47, pp. 12-25, 1998; page 13, incorporated by reference).

Regarding claim 28, Nelson et al. teach growing host cells containing cDNA inserts on microtiter plates prior to hybridization (page 210, third paragraph).

Regarding claim 29, Nelson et al. teach construction of a labeled probe library by reverse transcription of the polyA+ RNA isolated from normal human prostate tissue using oligo-dT-30 primer, reverse transcriptase, dATP, dTTP, dCTP, dGTP and ^{32}P-dCTP, in a reaction at 42 °C for 30 minutes. The filters were hybridized with the labeled probe, exposed to phosphor capture screens and the signals were quantitated on a phosphorimager (page 210, paragraphs 4-6).

Regarding claim 31, Nelson et al. teach sequencing of the members of the low abundance and high abundance clones (page 210, sixth paragraph; page 211, first paragraph; page 212, first paragraph).

Regarding claim 47, Nelson et al. teach that a cDNA library reflects transript diversity and redundancy of cellular mRNAs, of which 40-45% are rare transcripts, which therefore constitute about 30% of all cDNA clones in the non-normalized library.

B) Nelson et al. do not teach: a) selecting sub-groups of members of the non-normalized cDNA library represented in higher amounts, b) either the normalized or non-normalized libraries being full-length cDNA libraries, c) constructing a labeled probe library from a sub-group of members, hybridizing labeled probe library to a group of members and identifying members which

are not hybridized to the labeled probe library, and d) sequencing members of the cDNA library present in lower amounts and members of every subgroup, followed by pooling of all unique members. Nelson et al. teach that redundant clones can be pooled to comprise a secondary or tertiary generation probes for hybridization to array, and eliminate moderately abundant transcripts from further selection (page 214, second paragraph).

C) Regarding claim 15, Carninci et al. teach normalization of full-length cDNA libraries by hybridization of full-length cDNAs to biotinylated RNA, from which the cDNA has been obtained. The abundant cDNAs are removed by removing cDNA-RNA hybrids using magnetic beads with streptavidin. The resulting rare cDNAs are pooled (Fig. 1; page 1625, the last paragraph; page 1626, 1627; page 1628, paragraphs 1-6). The removed abundant cDNAs were stripped from the beads and re-used to prepare probe minilibraries (= selecting a first and subsequent groups of members of the non-normalized cDNA library present in higher amounts) (page 1620, second and third paragraphs; page 1627, paragraphs 8 and 9; Table 1). For example, the normalized library 26-100 from the whole embryo was prepared by hybridization with total starting RNA, followed by two rounds of hybridization with mini-libraries: ms1, minilibrary of liver, lung, brain and placenta, and Nm1, RIKEN non-redundant minilibrary (Table 1). The members of the cDNA library present in lower amounts and the subgroup members were pooled to form normalized libraries (Table 1).

Regarding claims 23 and 26, Carninci et al. teach full-length non-normalized and normalized libraries (page 1618, third paragraph; page 1621, fourth paragraph).

Regarding claim 30, Carninci et al. teach preparation of labeled probe minilibraries from selected subsets of abundant cDNAs (page 1627, paragraphs 9-12; page 1628, first and second paragraphs).

Regarding claims 31 and 44, Carninci et al. teach sequencing of the members of the libraries prepared by normalization with starting RNA and subtraction with probe minilibraries (page 1620, fourth paragraph; Table 1).

Regarding claim 43, Carninci et al. teach repeating steps of selecting the subgroups and identifying unique members of the subgroups. For example the normalized embryo library 56-304 was further contacted with the ms2 and Nm2 labeled subgroups (Table 1, page 1623).

Regarding claim 45, Carninci et al. teach pooling members of the cDNA library present in lower amounts and the subgroup members to form normalized libraries (Table 1).

Regarding claims 48-50, Carninci et al. teach libraries of whole body embryos, therefore they teach a sample from a plurality of different tissues, as well as RNA from a substantially every cell type from the same species of an organism (Table 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have combined the full-length cDNA library normalization method of Carninci et al. with a library normalization method of Nelson et al. The motivation to do so, provided by Carninci et al., would have been that the normalized cDNA library had a high percentage of full-length cDNAs which enhanced discovery of new genes (Abstract). Further, as stated by Carninci et al., "To avoid the problems related to amplification of libraries, we wanted to develop a technique to normalize and subtract cDNA before cloning. Published protocols did not lead to equal representation among clones of different sizes, maintain the length of long cDNAs after hybridization, or incorporate simultaneous normalization and subtraction of cDNAs."

8. Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nelson et al. (Genetic Analysis: Biomolecular Engineering, vol. 15, pp. 209-215, 1999; cited in the IDS and in the previous office action) and Carninci et al. (Genome Res., vol. 10, pp. 1617-1630, October 2000;

cited in the IDS; cited in the previous office action), as applied to claims 15-19 above, and further in view of Somerville et al. (Science, vol. 285, p. 380-383, 1999; cited in the previous office action).

A) Claim 20 is drawn to a plant cell being a soy, tobacco, wheat, rice or corn cell.

B) Nelson et al. and Carninci et al. teach construction of normalized full-length cDNA libraries from human prostate cells, but do not teach plant cells. However, Nelson et al. and Carninci et al. teach a method which is generally applicable to any type of cells and libraries constructed. Nelson et al. state that "...This procedure has several advantages over other methods such as normalization and subtraction for reducing the variation in abundance among the clones in a cDNA library. Standard library construction methods are employed without the necessity for PCR, reassociation reactions, or column purification of single-stranded DNA as used in several of the normalization and subtraction methods (citation omitted). Libraries previously made or purchased can be used without requiring new library construction." (page 214, second paragraph). In the Abstract, Nelson et al. point that "The identification of the entire complement of genes expressed in a cell, tissue or organism provides a framework for understanding biological properties and establishes a tool set for subsequent functional studies. The large-scale sequencing of randomly selected clones from cDNA libraries has been successfully employed as a method for identifying a large fraction of these expressed genes. However, this approach is limited by the inherent redundancy of cellular transcripts reflecting widely variant levels of gene transcription. As a result, a high percentage of transcript duplications are encountered as the number of sequenced clones accrues."

C) Somerville et al. teach sequencing of Arabidopsis thaliana and rice genome. Rice was chose because of its similarities with wheat, maize and other cereals. They also teach that it is

unlikely that other whole plant genomes would be sequenced because of the cost involved (page 380, third and fourth paragraphs).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have applied the library normalization method of Nelson et al. and Carninci et al. to rice and other plant genomes of Somerville et al. The motivation to do so, expressly provided by Nelson et al., would have been that library normalization permitted full elucidation of genes expressed in a given cell.

9. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nelson et al. (Genetic Analysis: Biomolecular Engineering, vol. 15, pp. 209-215, 1999; cited in the IDS and in the previous office action) and Carninci et al. (Genome Res., vol. 10, pp. 1617-1630, October 2000; cited in the IDS), as applied to claims 15-19 and 21 above, and further in view of El-Meanawy et al. (Am. J. Physiol. Renal Physiol., vol. 279, p. F383-F392, 2000; cited in the previous office action).

A) Claim 22 is drawn to a human cell being a kidney cell.

B) Nelson et al. and Carninci et al. teach construction of normalized cDNA libraries from human prostate cells, but does not teach human kidney cells. However, Nelson et al. and Carninci et al. teach a method which is generally applicable to any type of cells and libraries constructed. Nelson et al. state that "...This procedure has several advantages over other methods such as normalization and subtraction for reducing the variation in abundance among the clones in a cDNA library. Standard library construction methods are employed without the necessity for PCR, reassociation reactions, or column purification of single-stranded DNA as used in several of the normalization and subtraction methods (citation omitted). Libraries previously made or purchased can be used without requiring new library construction."

C) El-Meanawy et al. teach construction of mouse kidney expression libraries using the SAGE (serial analysis of gene expression) method. The library construction was the first step to analysis of gene expression in progressive kidney disease based on mouse model (Abstract, page F383). However, they point to the fact that SAGE does not provide reliable detection of transcripts with low abundance (page F390, second paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the library construction method of Nelson et al. and Carninci et al. to obtain clones from human kidney cell. The motivation to do so, expressly provided by El-Meanawy et al., would have been that expression libraries were a powerful tool to apply to elucidation of the mechanisms of renal disease because of the complexity of the disease and lack of effective treatments.

10. Claim 51 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nelson et al. (Genetic Analysis: Biomolecular Engineering, vol. 15, pp. 209-215, 1999; cited in the IDS and in the previous office action) and Carninci et al. (Genome Res., vol. 10, pp. 1617-1630, October 2000; cited in the IDS; cited in the previous office action), as applied to claims 15 and 48 above, and further in view of Xu et al. (Cancer Research, vol. 60, pp. 1677-1682, March 2000; cited in the previous office action).

A) Neither Nelson et al. nor Carninci et al. teach RNA sample from a plurality of different different individuals of the same organism.

C) Xu et al. teach normalization of prostate tumor and normal prostate tissue libraries (Abstract). Xu et al. teach a library generated from a pool of prostate tumor samples obtained from different clinical sources (page 1677, fourth paragraph; Table 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the RNA samples from plurality of different individuals of Xu et al. in the combined library normalization method of Nelson et al. and Carninci et al. The motivation to do so, provided by Xu et al., would have been that pooling resulted in identification of cancer-associated genes present in a small subpopulation of cancer patients (page 1681, 6th paragraph).

11. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

TS
May 24, 2004

JEFFREY FREDMAN
PRIMARY EXAMINER
5/25/04